

Attorney Docket No.: INT-0004  
Inventors: Mattern et al.  
Serial No.: 10/002,653  
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Remarks begin on page 7.

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**REMARKS**

Claims 1-13 are pending in the instant application. Claims 1-13 have been rejected. Claims 2, 3, 4, 5, 6, 7, 9 and 13 have been amended. Claims 1 and 10 have been canceled.

Reconsideration is respectfully requested in light of these amendments and the following remarks.

**I. Objection to Specification**

The Examiner has objected to the specification as containing embedded hyperlinks and/or other form of browser-executable code. Specifically, the Examiner refers to page 8, line 28 of the specification. It is respectfully pointed out, however, that the symbols shown at this page are not hyperlinks nor patent numbers, but rather, as made clear at this section of the specification, reference numbers for standardized sterilization protocols and/or validation tests well known to those skilled in the art. Thus MPEP §608.01 is not applicable in this case.

Withdrawal of this objection is therefore respectfully requested.

**II. Rejection of Claims 1-13 under 35 U.S.C. § 112, first paragraph**

Claims 1-13 have been rejected under 35 U.S.C. § 112, first

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paragraph. The Examiner has acknowledged the specification to be enabling for a scaffold/matrix and method for producing and using the scaffold matrix wherein the scaffold matrix comprises a collagen/glycosaminoglycan co-precipitate that has been cross-linked with glutaraldehyde at a density sufficient to stabilize the scaffold to terminal sterilization by exposure to E-beam radiation at about 15 to about 80 kGy so the scaffold matrix retains characteristics to function as a structural support for cell and tissue growth. However, the Examiner suggests that the specification does not provide enablement for any compositions containing collagen and glycosaminoglycan sterilized by any method and retaining any characteristics to function as any matrix or scaffold.

Thus, in an earnest effort to advance the prosecution of this case and in accordance with the Examiner's acknowledgment of enabled subject matter, Applicants have amended claim 13 to be drawn to a scaffold or matrix comprising a collagen and glycosaminoglycan co-precipitate cross-linked with glutaraldehyde at a density of cross-linkage which stabilizes the scaffold or matrix toward electron beam radiation at about 15 to about 80 kGy so that the matrix or scaffold retains characteristics to function as a structural support for cell and tissue ingrowth.

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Further, Applicants have canceled claim 1 and amended claims 2, 3, 4, 5, 6, 7 and 9 to ultimately depend from claim 13 and to mimic language of claim 13 acknowledged to be enabled by the Examiner by the instant specification. Claim 10 has been canceled in light of amendments to claim 13. The claims as amended are no longer drawn to any compositions containing collagen and glycosaminoglycan sterilized by any method and retaining any characteristics to function as any matrix or scaffold but rather specify that the invention is a scaffold or matrix of a collagen and glycosaminoglycan co-precipitate cross-linked by glutaraldehyde at a density of cross-linkage which renders it stable toward the sterilization technique of electron beam radiation at about 15 to about 80 kGy and which retains the specific characteristics to function as a structural support for cell and tissue ingrowth.

Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph is respectfully requested in light of these amendments.

**III. Rejection of Claims 1-13 under 35 U.S.C. § 112, second**

**paragraph**

Claims 1-13 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

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regards as the invention. Specifically, the Examiner suggests that bridging lines 1 and 2 of claim 1 stating "collagen a glycosaminoglycan" is unclear as to meaning and scope.

It is respectfully pointed out, however, that claim 1 has been canceled and claims 2, 3, 4, 5, 6, 7 and 9 have been amended to depend from claim 13. Claim 13 does not contain the language suggested to be unclear by the Examiner. Accordingly, these amendments render moot this rejection and withdrawal is respectfully requested.

IV. Rejection of Claims 1-13 under 35 U.S.C. § 103(a)

Claims 1-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Yannas et al. (U.S. Patent 4,060,081) or (U.S. Patent 4,280,954) in view of Cheung et al. The Examiner suggests that it would have been obvious to use gamma radiation for the sterilization of the cross-linked collagen/glycosaminoglycan matrix of Yannas et al. to obtain the advantage of this sterilization as disclosed by Cheung et al.

Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness toward the claimed invention, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to

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one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. See MPEP § 2143.

The combination of references cited by the Examiner in the instant rejection fails to meet all these criteria with respect to the claims.

At the outset, Applicants respectfully disagree with the Examiner regarding relevance of the teachings of Cheung et al. to the instant claimed invention. The teachings of Cheung et al. are related to collagen matrices, not cross-linked collagen/glycosaminoglycan matrices as claimed in the instant application. In addition, Cheung et al. teach use of gamma radiation, not electron beam radiation.

Further, Applicants respectfully disagree with the Examiner's characterization of the teachings of Cheung et al. Contrary to the Examiner's suggestion, the Abstract of Cheung et al. does not teach that at "1 Mrad dosage, insignificant damage occurred". Instead, Cheung et al. states in the Abstract that at 1 Mrad "less damage was caused to the collagen peptide backbone". This is contrasted in the Abstract to "significant damage" above

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such dosage. Further, Cheung et al. clearly questions effectiveness of the radiation at a dosage of 1 Mrad to completely sterilize a material. Accordingly, Applicants respectfully disagree with the Examiner's suggestion that Cheung et al. teaches advantages of gamma radiation sterilization when this reference clearly teaches some damage still occurs even at low doses where complete sterility is in question.

In addition, it is respectfully pointed out that the 1 Mrad dosage taught by Cheung et al. corresponds to 10 kGy. As discussed in Section II, *supra*, claims of the instant application have been amended to clarify that the scaffold or matrix is stable toward electron beam radiation at about 15 to about 80 kGy. Clearly the reference of Cheung et al., teaching some damage occurring at 1 Mrad or 10 kGy and "significant damage" above such dosage teaches away from any expectation whatsoever of a stable matrix or scaffold at greater dosages such as about 15 to about 80 kGy.

Further, Yannas et al. teaches standard cross-linking procedures such as set forth in Example 1 of the instant patent application. Experiments comparing cross-linked collagen/glycosaminoglycan matrices prepared in accordance with these standard cross-linking procedures with those prepared in

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accordance with the instant invention are described in the patent application at page 11, line 14 through page 13, line 8. Results from these experiments are also shown in Figures 1, 2 and 3. As shown therein, standard cross-linking procedures such as taught by Yannas et al. do not result in a scaffold or matrix as claimed which comprises a collagen and glycosaminoglycan co-precipitate cross-linked with glutaraldehyde at a density of cross-linkage which stabilizes the scaffold or matrix toward electron beam radiation at about 15 to about 80 kGy so that the matrix or scaffold retains characteristics to function as a structural support for cell and tissue ingrowth. In fact, the inability to terminally sterilize the material of Yannas et al. was the exact problem in the prior art which the instant invention was designed to overcome.

Accordingly, the scaffolds of Yannas et al. are different from the instant claimed invention. Thus, even if one of skill were motivated to try to use the gamma irradiation methods of Cheung et al. (despite teachings of damage even at lower doses of radiation than set forth in the claims herein and questions raised concerning efficacy of the sterilizing method) on the matrices of Yannas et al., they would not arrive at the instant claimed invention.

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Accordingly, the combination of cited references provides neither a motivation to combine their teachings nor any reasonable expectation of success with respect to the instant claimed invention. Further, the combination of prior art references does not teach or suggest a scaffold or matrix comprising a collagen and glycosaminoglycan co-precipitate cross-linked with glutaraldehyde at a density which stabilizes the scaffold or matrix toward electron beam radiation at about 15 to about 80 kGy so that the matrix or scaffold retains characteristics to function as a structural support for cell and tissue ingrowth as claimed, thus failing to teach or suggest all the claim limitations. Therefore, the combination of references fails to meet the criteria as set forth in MPEP § 2143 to establish a prima facie case of obviousness.

Withdrawal of this rejection is therefore respectfully requested.

v. Rejection of Claims 1-4, 12 and 13 under 35 U.S.C. § 102(b)

Claims 1-4, 12 and 13 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Yannas et al. (U.S. Patent 4,060,081) or (U.S. Patent 4,280,954). The Examiner suggests that the cross-linked collagen glycosaminoglycan matrix of Yannas et al. is inherently cross-linked sufficiently to retain

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characteristics after sterilizing as required by the claims.

Applicants respectfully traverse this rejection.

In accordance with MPEP § 2112, to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be recognized by persons of ordinary skill.

As discussed in Section IV, supra, Yannas et al. teach standard procedures for cross-linking which, contrary to the Examiner's suggestion, do not result in a scaffold or matrix as claimed which comprises a collagen and glycosaminoglycan co-precipitate cross-linked with glutaraldehyde at a density of cross-linkage which stabilizes the scaffold or matrix toward electron beam radiation at about 15 to about 80 kGy so that the matrix or scaffold retains characteristics to function as a structural support for cell and tissue ingrowth. This is clearly demonstrated by the comparative data presented in the instant application. Thus, contrary to the Examiner's suggestion, sufficient cross-linking to produce a matrix with the characteristics as claimed in the instant application is not inherent in Yannas et al. as sufficient cross-linking is demonstrated in the instant patent application to be missing from

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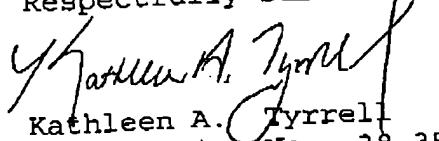
the matrices prepared in accordance with the teachings of Yannas et al. In fact, the inability to terminally sterilize the material of Yannas et al. was the exact problem in the prior art which the instant invention was designed to overcome.

Accordingly, the teachings of Yannas et al. do not anticipate the instant claimed invention and withdrawal of this rejection under 35 U.S.C. § 102(b) is respectfully requested.

#### VI. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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